Counterpoint: Oral Hypoglyemic Agents Should Be Used to Treat Diabetic Pregnant Women

It has now been established that even mild forms of gestational diabetes mellitus (GDM) (impaired glucose tolerance according to World Health Organization 1985 criteria) can cause major morbidity and even mortality if left untreated (1). As with type 2 diabetes, the prevalence of GDM has increased dramatically, linked to the worldwide obesity epidemic (2). This increase has been especially prevalent in the developing world and among indigenous populations who have adopted the unhealthy lifestyle of countries that are now part of the developed world (Maoris in New Zealand, Aborigines in Australia, and indigenous Americans in North America). The developing world, especially India but also Africa, faces an enormous increase in pregnant diabetic patients (both with GDM and with type 2 diabetes).

Specifically, Africa has neither the infrastructure nor the financial resources available to treat such large numbers of patients. If plans and appropriate protocols are not designed specifically for the needs of the pregnant population in these countries, there will be a marked increase in perinatal mortality and morbidity. It is especially the mortality, the severe birth injuries, respiratory distress syndrome, and neonatal hypoglycemia that cause concern in developing countries. Although large-for-gestational-age newborns are a very sensitive marker for good diabetic control, the prevention thereof is unlikely to be the top priority in poorly resourced countries.

Pathophysiology of GDM and type 2 (pregestational) diabetes

It is probable that insulin resistance is the main problem in these types of diabetes. In pregnancy, the maternal pancreas is unable to meet the increased demand of insulin that pregnancy requires and therefore cannot regulate the blood glucose levels within the narrow confines required. In pregnancy, although the fed state is prolonged, the glucose excursions remain in a narrow range.

Many GDM and type 2 diabetic patients are hyperinsulinemic, and it is illogical to just use more insulin, leading to further obesity. A drug that alters insulin sensitivity is therefore more logical. If the lowering of insulin resistance can result in maternal blood glucose levels closer to normal values, morbidity and mortality would be reduced.

Safety of oral hypoglycemic agents in pregnant women

Coustan (3) outlined the guiding principles that any clinician should consider before using pharmacological agents in pregnancy. Safety for mother and fetus are paramount, and the benefits must obviously outweigh the risks. A key consideration is whether the substance crosses the placenta and, if it crosses, whether it will harm the fetus. Insomuch as oral hypoglycemic agents (OHAs) can normalize the hyperglycemia that harms the fetus, they must be beneficial. However, sulfonylureas stimulate insulin secretion from the fetal β-cells, thereby potentially increasing the harmful hyperinsulinemic effects in the fetus caused by hyperglycemia.

In 1974, Prof. W.P.U. Jackson and myself were confronted with a large population of GDM and pregestational type 2 diabetic patients who were traditionally poorly controlled and who abhorred the thought of injecting themselves with insulin. The results were high perinatal mortality and morbidity. In an attempt to improve the situation, they elected to use glibenclamide (a relatively short-acting sulfonylurea) and metformin (a biguanide relatively free of the problems of lactic acidosis).

An audit of mothers who had received OHAs in the first trimester (because their pregnant state was unknown) demonstrated an association between fetal anomalies and hyperglycemia rather than OHAs (4). These drugs were therefore introduced into the protocol and, after over a decade of use, were audited and the results published (5,6). Especially in GDM, the perinatal mortality (PNM) was dramatically reduced. Although an acceptable control group was not identified, the PNM of patients who did not receive treatment to normalize hyperglycemia was up to 10 times greater than that of patients who had been treated with a graduated regimen from diet to OHAs to insulin. However, overwhelming world opinion was against the use of OHAs, thus ignoring the plight of millions of women in poorly resourced countries who did not have access to insulin for various reasons. The reasons given were fear of teratogenicity to the fetus, metabolic effects on offspring, and lack of randomized studies to demonstrate the equivalence of an OHA-based protocol to an insulin-only protocol for treatment.

When the enormity of the burden of GDM and type 2 diabetics was recognized worldwide, some interest in an alternate mode of treatment was stimulated. Langer et al. (7) produced the first and only published randomized trial to date in 2000 comparing glyburide (glibenclamide) to insulin. They studied 404 women with GDM (201 received glyburide, and 203 received insulin), and from their data they concluded that glyburide was a clinically effective alternative to insulin. Since then there have been numerous publications of studies in which glibenclamide has been used (8–10).

Moore (11) reviewed five retrospective reports of glyburide treatment for GDM and analyzed 504 pregnant patients who had been treated with glyburide. In summary, he reported that the failure rate for glyburide treatment was ~20%. Mean maternal fasting glucose and postprandial values were lower in glyburide-treated patients, but this was accompanied by fewer patients having asymptomatic hypoglycemia (63% in insulin-treated and 28% in glyburide-treated patients) (12).

The rate of neonatal hypoglycemia and hyperbilirubinemia was possibly increased (but did not reach statistical significance). There was not an increase in birth weight or macrosomia in the glyburide group. He felt the need for better pharmacodynamic studies specifically in pregnancy with chronic therapy. He recommended that glyburide should be given 1 h before a meal and that it can be used up to three times per day. All studies followed Langer's protocol and used up to 20 mg glyburide per 24 h (a dose that is, in our opinion, seldom or never indicated). Langer also studied the transfer of

glyburide to the fetus. He found no evidence that any drug was transferred. Elliot et al. (13) demonstrated minimal transfer of glyburide over the placenta.

Concerning metformin, there were no randomized studies published until recently. This will be rectified when the results of a randomized study of metformin use in GDM (the MiG Study) are presented (14). Coetzee and Jackson published studies on the use of metformin in pregnant patients and reported excellent PNM results (15).

The use of metformin was introduced in patients with polycystic ovarian syndrome, which is associated with insulin resistance. With metformin, many of these patients ovulated and became pregnant. For optimum results, most endocrinologists continued treatment into the first trimester. Subsequently, Glueck et al. (16) continued their treatment with metformin throughout pregnancy in 90 women. They concluded that metformin reduced the prevalence of GDM, appeared to be safe for mother and fetus, and was not associated with preeclampsia in pregnancy with polycystic ovarian syndrome.

Hughes and Rowan (17) reviewed data from 214 pregnant type 2 diabetic subjects; 93 were on metformin, of whom 32 continued until delivery. They concluded that the women treated with metformin had more risk factors for adverse pregnancy outcomes, but no differences in outcomes were seen between those taking or not taking metformin.

Rowan et al. (14) have concluded the Metformin in Gestational Diabetes Trial, in which 512 women were recruited. A detailed interim analysis of 200 recruits was reviewed by the data safety monitoring committee. They could not detect any safety concerns or reasons for changing the protocol.

In a recent audit of Cape Town, South Africa, data in pregnant patients with type 2 diabetes, metformin alone was not associated with increased PNM (18). The data on GDM at Groote Schuur Hospital (Groote Shuur, South Africa) have also been reviewed, and no PNM occurred in patients using metformin singly or in combination with glibenclamide (19).

Metformin does cross the placenta, but it is not an insulin secretogog; rather, it enhances insulin action. Long-term studies of offspring are therefore required, and this is included in the Metformin in Gestational Diabetes Trial protocol (12). Hague et al. measured plasma metformin levels in seven mothers taking 2,000 mg daily (20). The fetal concentration of metformin was approximately one-half that of maternal levels.

In addition, Moore (11) postulated that the pharmacokinetics of a drug may be altered in pregnancy and from individual to individual. Patients with p450 gene polymorphisms might, for instance, have potentially differing rates of glyburide metabolism.

The future

Evidence is slowly emerging that OHAs, when used carefully and judiciously, can be included in the management of GDM and possibly some cases of type 2 diabetes. In poorly resourced countries, the benefit of using OHAs specifically in GDM far outweighs the risks that might be associated with their use. Insulin needs ideal storage conditions, which are not always available in developing countries. OHAs should be seriously considered where diabetes educators are a rare resource, where insulin is expensive or not available, and where low levels of literacy make it difficult to explain the intricacies of using insulin appropriately. Evidence has been published that hypoglycemia is less of a problem when using glyburide compared with insulin therapy and therefore safer for the mother (12).

Studying world literature, it is obvious that despite the exclusive use of insulin, the goals of the St. Vincent Declaration are still only a vision and not a reality. The prevalence of congenital anomalies resulting in more frequent terminations of pregnancy or in death of the offspring remains a problem (21). Better preconception counseling and diabetes control before conception are the answers to the latter—as opposed to concern whether the patient is well controlled on insulin or OHAs.

Macrosomia continues to be a problem in diabetic pregnancies. Tighter blood glucose control has been shown to improve the prevalence of macrosomia. Often, this is not achieved with human insulin protocols, but with the availability of insulin analogs euglycemia can be achieved more easily. However, the expense of insulin analogs has to be taken into consideration. The suggested target is to obtain a 90-min postprandial blood glucose value <6.7 mmol/l (120 mg/dl) (22).

Even with an excellent knowledge of the pharmacokinetics of OHA's and taking into account the individual variable metabolism of these agents, it is probably not possible to obtain the same pin-point accuracy in achieving this goal on OHAs. As macrosomia can be correlated with the postprandial glucose excursion (especially the peak postprandial value), there might be a greater prevalence of macrosomia associated with using OHAs. In the 1988 review on OHAs in GDM by Coetzee and Jackson (6), glibenclamide did have the highest prevalence of large-for-gestational-age infants (22%), but diabetic mothers whose hyperglycemia was untreated had a 38% prevalence of macrosomia, demonstrating that hyperglycemia was the more powerful etiologic factor in causing macrosomia. As there is still a paucity of data on the use of OHAs in pre-GDM, extra caution is recommended.

Conclusions

Hyperglycemia is the strongest factor implicated in fetal and newborn mortality and morbidity associated with diabetes. The Hyperglycemia and Adverse Pregnancy Outcome Study has demonstrated that morbidity risk related to hyperglycemia is a continuum and that a safe level of hyperglycemia cannot be presumed (23).

In type 1 diabetes, there is no choice in management protocols. However, especially in gestational diabetes, but possibly also in type 2 (pregestational) diabetes, there is a place for OHAs. This is particularly so in poorly resourced countries where the price and lack of insulin may be important factors. There is evidence that good results can be achieved with OHAs providing that euglycemia targets are achieved. The ease of education, administration, and management of these selected pregnant diabetic patients make the use of OHAs an attractive option, especially in a poorly resourced environment.

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References

1. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS, the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group: Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *N Engl J Med* 353:2477–2486, 2005
2. Ferrara A: Increasing prevalence of gestational diabetes mellitus. *Diabetes Care* 30 (Suppl. 2):S141–S146, 2007
3. Coustan DR: Pharmacological management of gestational diabetes. *Diabetes Care* 30 (Suppl. 2):S206–S208, 2007
4. Coetzee EJ, Jackson WPU: Oral hypoglycaemics in the first trimester and fetal outcome. *S Afr Med J* 65:635–637, 1984
5. Coetzee EJ, Jackson WPU: The management of non-insulin-dependent diabetes during pregnancy. *Diabetes Res Clin Pract* 1:281–287, 1986
6. Coetzee EJ, Jackson WPU: Oral hypoglycemia agents in the treatment of gestational diabetes. In *Controversies in Diabetes and Pregnancy, Endocrinoloy and Metabolism*. Jovanovic L, Ed. New York, Springer-Verlag, 1998, p. 57–76
7. Langer O, Conway DL, Berkus MD, Xenakis EM, Gonzales O: A comparison of glyburide and insulin in women with gestational diabetes mellitus. *N Engl J Med* 343:1134–1138, 2000
8. Kremer CJ, Duff P: Glyburide for the treatment of gestational diabetes. *Am J Obstet Gynecol* 190:1438–1439, 2004
9. Jacobson GF, Ramos GA, Ching JY, Kirby RS, Ferrara A, Field DR: Comparison of glyburide and insulin for the management of gestational diabetes in a large managed care organization. *Am J Obstet Gynecol* 193:118–124, 2005
10. Chmait R, Dinise T, Moore T: Prospective observational study to establish predictors of glyburide success in women with gestational diabetes. *J Perinatol* 24:617–622, 2004
11. Moore TR: Glyburide for the treatment of gestational diabetes. *Diabetes Care* 30 (Suppl. 2):S209–S213, 2007
12. Yogev Y, Ben-Harousn A, Chen R, Rosenn B, Hod M, Langer O: Undiagnosed asymptomatic hypoglycaemia: diet insulin and glyburide for gestational diabetic pregnancy. *Obstet Gynecol* 104:88–93, 2004
13. Elliott BD, Langer O, Schenker S, Johnson RF, Prihoda T: Comparative placental transport of oral hypoglycaemic agents in humans: a model of human placental drug transfer. *Am J Obstet Gynecol* 171: 653–660, 1994
14. Rowan JA, the MiG Investigators: A trial in progress: gestational diabetes: treatment with metformin compared with insulin (the Metformin in Gestational Diabetes [MiG] trial). *Diabetes Care* 30 (Suppl. 2): S214–S219, 2007
15. Coetzee EJ, Jackson WPU: Metformin in management of pregnant insulin-independent diabetics. *Diabetologia* 16:241–245, 1979
16. Glueck CJ, Bornovali CJ, Pranikoff J, Goldenberg N, Dharashivkar S, Wang P: Metformin, pre-eclampsia and pregnancy outcomes in women with polycystic ovary syndrome. *Diabet Med* 21:829–836, 2004
17. Hughes RCE, Rowan JA: Pregnancy in women with type 2 diabetes: who takes metformin and what is the outcome? *Diabet Med* 23:318–322, 2006
18. Ekpebegh CO, Coetzee EJ, van der Merwe L, Levitt NS: A 10 year retrospective analysis of pregnancy outcome in pre-gestational type 2 diabetes: comparison of insulin and oral glucose-lowering agents. *Diabet Med* 24:253–258, 2007
19. Coetzee EJ, Ekpebach C, Levitt NS: Combined use of metformin and glibenclamide in gestational and type 2 diabetics. Program and abstract presented at the 4th International Symposium on Diabetes and Pregnancy, 29–31 March 2007 at the Hilton Istanbul hotel, Istanbul, Turkey
20. Hague WM, Davoren PM, McIntyre D, Norris R, Xiaonian X, Charles B: Metformin crosses the placenta: a modular for fetal insulin resistance (Letter)? *Br Med J*. 4 December 2003. [Epub]
21. Confidential Enquiry into Maternal and Child Health Diabetes in Pregnancy: Are we providing the best care? Findings of a National Enquiry: England, Wales and Northern Ireland, 2007. London, Confidential Enquiry into Maternal and Child Health Diabetes in Pregnancy, 2007
22. Ben-Haroush A, Yogev Y, Chen R, Rosenn B, Hod M, Langer O: The postprandial glucose profile in the diabetic pregnancy. *Am J Obstet Gynecol* 191:576–581, 2004
23. Hampton T: Medical news and perspectives: study finds newborn outcomes affected by blood glucose levels during pregnancy. *JAMA* 298:613–614, 2007